CAPRISA

CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA

INSTI's FOR THE MANAGEMENT OF HIV-ASSOCIATED TB (INSIGHT STUDY)

Statistical Analysis Plan (SAP)

for

INSIGHT Protocol (Ver 3.0, dated 04 July 2022)

Revised as of 28 July 2023

A phase 2b study to evaluate the efficacy, safety, and pharmacokinetics of a combination of Bictegravir, Emtricitabine, and Tenofovir Alafenamide Fumarate for treatment of HIV-1 infection in patients with drug-susceptible tuberculosis on a Rifampicin-based treatment regimen:

A Phase 2b Open-label Randomised-Controlled Trial

Doris Duke Medical Research Institute (2nd floor), 719 Umbilo Road, Private Bag X7, Congella, 4013, Durban, South Africa
tel: +27 31 2604555 | **fax**: +27 31 2604549 | email: **caprisa@caprisa.org** | **www.caprisa.org**

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Trial full title	INSTI's FOR THE MANAGEMENT OF HIV-ASSOCIATED TB: A phase 2b study to evaluate the efficacy, safety, and pharmacokinetics of a combination of Bictegravir, Emtricitabine, and Tenofovir Alafenamide Fumarate for treatment of HIV-1 infection in patients with drug-susceptible tuberculosis on a Rifampicin-based treatment regimen (CAP093)
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Trial principal investigator	Dr Anushka Naidoo
SAP author(s)	Marothi Peter Letsoalo

II. SAP SIGNATURE

Statistician (Author)

Name: Mr Marothi Peter Letsoalo

Signature:

Date: 25/11/2023

Principal Investigators

Name: Dr Anushka Naidoo

Signature:

Date: 25/11/2023

Co-Principal Investigator

Name: Prof. Kelly E Dooley

Signature:

Date: 11.30.2023

III. LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definitions
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AT	As Treated
BIC	Bictegravir
BMI	Body Mass Index
BP	Blood Pressure
CC	Complete Case
CI	Confidence Interval
CRF	Case Report Form
DTG	Dolutegravir
FDA	Food and Drug Administration
FTC	Emtricitabine
IQR	Interquartile range
ITT	Intention to Treat
MAR	Missing at Random
MCAR	Missing Completely at Random
mITT	modified Intention to Treat
MNAR	Missing Not at Random
PK	Pharmacokinetics
PP	Per Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SE	Standard Error
TAF	Tenofovir alafenamide

1 INTRODUCTION

1.1 PREFACE

The INSIGHT study is being conducted to assess the antiretroviral activity of a fixed-drug, single-tablet, combination of Bictegravir 50mg/ Emtricitabine 200mg/ Tenofovir alafenamide 25mg (Biktarvy®) dosed twice daily in HIV-1 infected, ART-naïve and ART non-naïve patients with TB co-infection receiving rifampicin-based tuberculosis (TB) treatment regimen. This study will assess the activity of Bictegravir and dolutegravir-containing ART regimens in patients with drug-susceptible TB for 48 weeks. The purpose of the INSIGHT study is to evaluate the efficacy, safety, and pharmacokinetics of a combination of Bictegravir, Emtricitabine, and Tenofovir Alafenamide Fumarate for the treatment of HIV-1 infection in patients with drug-susceptible tuberculosis on a Rifampicin-based treatment regimen.

1.2 SCOPE OF THE ANALYSIS PLAN

The analyses that will be performed for the INSIGHT study are outlined in this Statistical Analysis Plan (SAP). The purpose of this SAP is to provide guidance for Biostatisticians and Statistical Programmers who will analyse the data (Heeley, et al., 2016). The analyses described in this SAP may appear in study data monitoring report, regulatory submissions, or future publications. To understand the study design and procedures, the reader of this SAP should also refer to the clinical protocol version 3.0 dated 04 July 2022 (NCT04734652) and other relevant documents.

2 STUDY OBJECTIVES AND CLINICAL ENDPOINTS

The INSIGHT study intends to assess the efficacy, safety, and pharmacokinetics of twice daily, co-formulated BIC 50mg/FTC 200mg/TAF 25mg in HIV positive patients not currently on ART who have drug susceptible tuberculosis and are receiving a rifampicin-based regimen in South Africa.

2.1.1 Primary objective and endpoint

Objective: To characterize viral suppression rates (proportion of patients with HIV VL<50) at week 24 in the BIC/FTC/TAF arm.

Endpoint: Proportion of patients with suppressed viral load (HIV-1 RNA <50 copies/mL) at week 24 in the BIC arm (as per FDA snapshot algorithm).

2.1.2 Secondary objectives and endpoints

A. **Objective**: To characterize viral suppression rates (proportion of patients with HIV VL<50) at weeks 12, 24 and 48 in the standard of care treatment (SOC) arm (currently, TDF 300mg/3TC 300mg/DTG 50mg) and at weeks 12 and 48 in the BIC/FTC/TAF arm.
   Endpoint: Viral suppression rates (HIV-1 RNA <50 copies/mL) at weeks 12, 24 and 48 in the DTG arm and at 12 and 48 weeks in the BIC arm
B. **Objective:** To compare the pharmacokinetics (PK) of BIC when given twice daily and co-administered with rifampicin during tuberculosis treatment vs when given alone after discontinuation of rifampicin.
   Endpoint: PK of BIC when given twice daily and co-administered with rifampicin during TB treatment vs when given alone after TB treatment completion
C. **Objective:** To assess the incidence of TB associated IRIS in each arm, through week 24.
   Endpoint: Incidence of TB associated IRIS through week 24, by Arm
D. **Objective:** To characterize the tolerability of treatment in each arm by assessing frequency of clinician-initiated treatment interruptions or switches through week 48.
   Endpoint: Grade 3 or higher AEs, SAEs; clinician-initiated treatment interruptions or switches through week 48.
E. **Objective:** To assess frequency of ART drug resistance mutations in participants with detectable viral load at study visit weeks 24 and 48.
   Endpoint: Frequency of ART drug resistance mutations in participants with detectable viral load at weeks 24 and 48.

2.1.3 Exploratory objectives and endpoints

A. **Objective:** To determine the effects of pharmacogenetics (genetic variability in drug metabolising enzymes or drug transporters including but not limited to UGT1A, p-glycoprotein) on BIC/FTC/TAF.
   Endpoint: Effects of pharmacogenetics of drug metabolising enzymes or drug transporters (e.g., UGT1A1, CYP3A, p-gp) on BIC/FTC/TAF/ PK.
B. **Objective:** To compare the pharmacokinetics (PK) of TAF, intracellular TFV-DP, FTC and DTG when given twice daily and co-administered with rifampicin during tuberculosis treatment vs when given alone after discontinuation of rifampicin.
   Endpoint: PK of FTC, TAF, and intracellular TFV-DP when given twice daily and co-administered with rifampicin during TB treatment vs when given alone after TB treatment completion
C. **Objective:** To determine the PK of TB drugs.
   Endpoint: PK of TB drugs

D. **Objective:** To describe the PK in hair of BIC, FTC, TAF during and after co-treatment with Rifampicin.
   Endpoint: Association between hair PK during and after co-treatment with rifampicin
E. **Objective:** To describe maternal and fetal outcomes among women who become pregnant on study.
   Endpoint: Maternal and fetal outcomes

3 STUDY METHODS

3.1 GENERAL STUDY DESIGN AND PLAN

The INSIGHT study is a phase 2b open-label non-comparative randomised-controlled trial among HIV positive, ART naïve and ART non-naïve, adult patients (>18 years) with drug-sensitive TB who are receiving a rifampicin-based first-line TB regimen. The study intends to assess the efficacy, safety, and pharmacokinetics (PK) of twice daily, co-formulated Bictegravir (BIC) 50mg/ Emtricitabine (FTC) 200mg/ Tenofovir alafenamide (TAF) 25mg and to characterize viral suppression rates at week 24 through to week 48 in the BIC/FTC/TAF arm. A concurrent control arm in which participants receive a dolutegravir-based regimen will also be enrolled.

3.2 INCLUSION-EXCLUSION CRITERIA AND GENERAL STUDY POPULATION

3.2.1 Inclusion criteria

a. Adults ≥ 18 years of age with Karnofsky score ≥ 70
b. Confirmed rifampicin-susceptible tuberculosis and/or
c. On first-line rifampicin-based tuberculosis treatment (not > 8 weeks at the time of enrolment)
d. Documented HIV-1 infection, ART-naïve OR ART non-naïve (patients to have no exposure to ART medication at least ≥ 3 months at the time of enrolment)
e. Estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73m^2
f. Alanine aminotransferase (ALT) ≤3 times the upper limit of normal (ULN)
g. Total bilirubin ≤2.5 times ULN
h. Creatinine ≤2 times ULN
i. Haemoglobin ≥ 7.0 g/dL (6.5 g/dL for females)
j. Platelet count ≥ 50,000/mm3
k. Absolute Neutrophil Count (ANC) ≥650/mm3
l. Able and willing to provide written informed consent.

m. Female patients agree to use both a barrier and a non-barrier form of contraception during the study, starting at least 14 days prior to enrolment.

3.2.2 Exclusion criteria (at the time of screening)

a. Pregnancy or breastfeeding (or planned pregnancy within 12 months of study entry)
b. Prior use of antiretroviral drugs for pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP) < 3 months at the time of enrolment
c. Hepatitis B surface antigen positive OR Hepatitis B virus (HBV) infection OR active systemic infections (other than HIV-1 infection) requiring systemic antibiotic or antifungal therapy current or within 30 days prior to baseline that could, in the opinion of the investigator, interfere with study procedures or assessment of study outcomes.
d. Participants with a CD4+ cell count of < 50 cells/ µl
e. Any verified Grade 4 laboratory abnormality, with the exception of, Grade 4 triglycerides. A single repeat test is allowed during the Screening period to verify a result.
f. Patients on metformin (> 500mg, 12hourly)
g. Patients with an uncontrolled psychiatric co-morbidity. Patients who, in the investigator's judgment, pose a significant suicidality risk. Recent history of suicidal behaviour and/or suicidal ideation may be considered as evidence of serious suicide risk.
h. Other condition or circumstance deemed by clinician/investigators to be detrimental to patient safety or study conduct.
i. Unwilling to be part of the main pharmacokinetic (PK) study and have PK blood draws done (NB there is a semi-intensive PK sub-study which is optional)

NOTE: All potential participants will undergo screening evaluations to determine eligibility. The principal investigator (or designate) will assess eligibility and ensure that the participant meets all the inclusion criteria. Participants may be deemed ineligible at the discretion of the principal investigator or designated based on safety or other criteria.

3.3 RANDOMIZATION AND BLINDING

Patients will be screened at a single site and those deemed eligible will be randomized in a 2:1 ratio to Intervention/BIC arm (n=80) or to a non-comparative Control/DTG arm (n=40). Participants will be randomized according to a predetermined random order by the study statistician. The computer-generated randomisation list will be generated by a statistician, where random permutation blocks of varied sizes will be used. Either opaque sealed envelopes or an electronic randomisation system will be used for study arm allocation. The

envelopes will be stored in a locked cupboard and opened in sequential order by study team members authorized to perform randomization procedures by the Principal Investigator. In the case of electronic randomisation, the password protected randomization list will be sent to the data manager so that it can be uploaded into the database. The study will be open label.

4 SAMPLE SIZE DETERMINATION

The study is not designed to compare primary and secondary outcomes between the two study arms. Rather, the sample size is based on precision for estimating the response rate in the BIC arm, following a similar design in the REFLATE and INSPIRING trials.

Table 1: ***Sample Size Determination***

Item or Parameter	Assumed value
BIC/FTC/TAF response rate	**85%** *This is the expected proportion of patients who will have a successful response to the BIC/FTC/TAF treatment, which is defined as having an HIV viral load of less than 50 copies/mL at week 24.*
DTG response rate (non-comparator group)	**70%** This is the expected proportion of patients who will have a successful response to the DTG treatment, which is used as a reference group but not as a direct comparator. The test assumes that this response rate is 70%, based on previous studies.
Statistical Test	**1-sided 95% upper CI** A one-sided 95% upper confidence interval means that the test will estimate the upper limit of the range of values that contains the true difference with 95% confidence.
Hypothesis formulation	**H_0: $\pi \leq 0.70$;** **H_1: $\pi > 0.70$** H_0 is the null hypothesis, which assumes that there is no difference between the response rates of the two treatments, or that the response rate of BIC/FTC/TAF is less than or equal to 0.70. H_1 is the alternative hypothesis, which assumes that the response rate of BIC/FTC/TAF is greater than 0.70.)
Type I error Rate	**α=0.05**

Item or Parameter	Assumed value
	The test will use a type I error rate of 0.05, which means that there is a 5% chance of making this error.
Power	β>85% The test will have a power of more than 85%.

The power calculation was performed using the SAS POWER procedure for an exact test for a binomial proportion. The test is one-sided, with the null hypothesis being that the proportion is less than or equal to 0.7. The nominal alpha level is set at 0.05. The alternative hypothesis is that the proportion is equal to 0.85. The power of the test was calculated for two different sample sizes of n=66 and n=80. For a sample size of 66, the actual alpha level is 0.0414, and the power of the test is 0.890 while for a sample size of 80, the actual alpha level is 0.0302, and the power of the test is 0.916. Based on these results, we can conclude that with a sample size of 66 to 80 and assuming an 85% response rate for BIC/FTC/TAF at week 24, we have sufficient power (greater than 85%) to detect a response rate of greater than 70% of the DTG. The sample size has been chosen to provide an adequate number of participants for assessing the antiretroviral activity of BIC/FTC/TAF. A non-comparative control group of 30-40 patients will be enrolled in the DTG arm to provide safety and efficacy parameters for standard-of-care treatment in the local setting, to contextualize the BIC arm results and to serve as a baseline comparator group for safety and efficacy parameters. The study will enrol a minimum of 120 participants.

5 GENERAL ANALYSIS CONSIDERATIONS

5.1 STUDY ASSESSMENTS AND TIMING OF ANALYSES

After randomisation, participants are scheduled follow-up visits at week 4, 8, 12, 24, 32, 40 and 48. Section 7.1 of the INSIGHT study protocol documents the full schedule of events (SOE). The FDA snapshot algorithm will be used for the data analysis window of virological outcome. For all other outcomes, the study visit window will be followed, unless otherwise specified.

Table 2: Schedule of important study assessments related to the study objectives.

	Follow-up (in weeks)						
Study visit	**4**	**8**	**12**	**24**	**32**	**40**	**48**
Target day of visit	28	56	84	168	224	280	336
Study Assessment windows in days	±7	±7	±7	±14	±14	±14	±14
AEs/SAEs assessment	✓	✓	✓	✓	✓	✓	✓
TB associated IRIS Assessment	✓	✓	✓				
PK blood draws[2] PK dry blood spots[3]	✓	✓	✓	✓	✓		✓
Virologic Outcome window in days			**63-105**	**127-210**			**295-378**
HIV-RNA viral load[1]	✓	✓	✓	✓		✓	✓

[1] "If viral load detectable any time after week 24 or at week 24 or 48 participants may be counselled and a VL retest may be done 2-4 weeks later."
[2] "The protocol specifies the sampling timepoints and required visits for PK sampling and DBS for each arm. Additionally, the semi-intensive PK sub-study has its own specified sampling timepoints."

5.2 ANALYSIS POPULATION

5.2.1 Intention-to-Treat (ITT)

The ITT analysis population consists of all randomized participants.

5.2.2 Modified Intention-to-Treat (mITT)

The mITT population preserves the randomization and intention-to-treat principles while allowing for some flexibility in the analysis. This population includes all randomized participants who received at least one dose of the study drug, regardless of attendance of post-enrolment study visits who have drug-sensitive TB, and who were on rifampicin-based TB treatment. The mITT population excludes participants who were erroneously randomized or did not meet eligibility criteria. Unless stated differently, the study will use the ITT/mITT analysis population to assess all endpoints. As per the protocol, the mITT analysis population is the primary analysis population for the primary endpoint.

5.2.3 As-Treated (AT)

The AT population will be used for analysis should there be a case where a participant has not received the treatment they were randomised to, thus the analysis will follow the actual treatment that the participants received. In this case the ITT/mITT analysis may not show the true effect of the treatment, so the AT analysis can confirm the ITT/mITT results by showing how the treatment worked. This can help to evaluate the endpoint in case some participants received a treatment other than what they were randomized to. Unless stated differently, the study will use the AT analysis population to assess all endpoints.

5.2.4 Per-Protocol (PP)

The PP population includes only those participants who strictly adhered to the study protocol and completed the study without major protocol violations.

5.2.5 Safety

This population includes all participants who received at least one dose of the study drug and have at least one post-baseline safety assessment. Participants who did not complete the study or had major protocol deviations may also be included.

5.2.6 Other analysis population

- PK concentration population defined as all enrolled subjects who received at least one dose of the study and in whom at least one concentration value is reported.

- The PK parameter population defined as all enrolled subjects who received at least one dose of the study and had at least one derived value of a specific PK parameter.

5.3 PROTOCOL DEVIATIONS

The prespecified deviation/violation of enrolling a participant who did not meet all eligibility criteria will exclude a participant from ITT/mITT (and, if applicable, AT) and PP analyses, as they may do not represent the target population or may have a different risk-benefit profile for the intervention.

The following protocol violations may exclude a participant from PP analysis due to the reason of

- ***product dispensation error***, as they may have received a different intervention than assigned or intended.
- ***omission of a required procedure***, as they may not have completed the trial according to the protocol.
- ***conduct of non-protocol procedure***, as they may have received an intervention that was not specified in the protocol.
- ***conduct of study visit outside visit window***, as they may have deviated from the protocol schedule.
- ***use of expired test kit***, as they may have received an unreliable or invalid test result.

5.4 COVARIATES AND SUBGROUPS

The following variables or subgroups are identified and known to have an important influence on specific endpoints:

Variable/Subgroup	Variable Type	Expected Influence
a) Age	Continuous	Age can affect the efficacy of the antiretroviral therapy (ART) and TB treatment, as well as the immune system's ability to control HIV.
b) Sex	Categorical	Sex differences can influence the response to ART and TB treatment, and women may have higher rates of adverse drug reactions.
c) Treatment group	Binary	Treatment groups BIC/FTC/TAF and dolutegravir-based regimen (DTG) will be used as subgroups rather than for comparison.
d) Baseline HIV viral load	Continuous	The initial level of HIV viral load is a strong predictor of treatment success, and it has a potential to assess the effectiveness of ART.

e) Baseline CD4 cell count	Continuous	The baseline CD4 cell count is an important predictor of HIV progression and can also affect the immune response to TB.
f) Adherence to ART g) Adherence TB treatment	Categorical	Poor adherence to ART and TB treatment can lead to treatment failure and the development of drug-resistant strains of HIV and TB
h) Prior TB treatment	Binary	Previous treatment with ART and TB drugs can affect the response to current therapy and increase the risk of drug resistance.
i) Co-morbidities	Binary	The presence of other medical conditions that can affect the immune system's ability to control HIV and TB.
j) HIV drug resistance k) TB drug resistance	Binary	Resistance to ART and TB drugs can reduce treatment efficacy and increase the risk of treatment failure.
l) Body mass index (BMI)	Continuous	BMI can affect the pharmacokinetics and efficacy of antiretroviral and TB drugs.
m) Duration of TB treatment	Continuous	The length of TB treatment can affect the response to ART and the risk of drug interactions.

Continuous variable will be further categorised by the investigator to form clinical meaningful groups.

5.5 DERIVED VARIABLES

5.5.1 Primary outcome and other secondary outcome variables

- Virologic outcome variable is a categorical variable which will be computed according to the FDA snapshot algorithm (Food and Drug Administration, 2015). The FDA snapshot algorithm is a method for analyzing the efficacy of antiretroviral drugs for the treatment of HIV-1 infection (Food and Drug Administration, 2015). It classifies subjects into one of four mutually exclusive categories based on their virologic response and use of study drug at a specific time point, such as week 12, 24, and 48. The categories are:
  i. Virologic success: Subjects who have HIV-1 RNA levels below a predefined threshold (such as <50 copies/mL) and are on study drug at the time point of interest.
  ii. Virologic failure: Subjects who have HIV-1 RNA levels above the threshold, have discontinued study drug because of lack of efficacy, have had confirmed virologic rebound, or have died.

iii. No virologic data: Subjects who have no HIV-1 RNA measurements in the window around the time point of interest but are still on study drug.

iv. Discontinued study drug: Subjects who have discontinued study drug for reasons other than virologic failure or death, such as adverse events, noncompliance, or withdrawal of consent.

- Grade 3 or higher AEs will be a binary variable created from a variable in the database indicating the presence of each AE grade (grade 1 - 5). This binary variable will record "yes" for participants with adverse events that are grade 3 or higher and "no" otherwise.
- Tolerability will be assessed by Clinician-initiated treatment interruptions or switches.

5.5.2 Covariates and subgroups

- Baseline viral load will be categorized as at most 100,000 and above 100,000 copies/ml.
- CD4 count will be categorized as CD4 count of a participant less than 100 cells/mm^3 to make a binary variable.
- BMI will be calculated with the study database as metric units by dividing the weight in kilograms with the square of height in meters.

5.6 MISSING DATA

The study protocol employs the FDA snapshot algorithm for the primary endpoint. As such, the virologic response may be categorized as *No virologic data* or *Discontinue study drug*. If the number of participants in these categories at least 5% of the minimum required sample size (n=66), multiple imputation will be used under the assumption that the data are missing at random (Little, et al., 2012). This means that it is assumed that these values can be predicted from all observed data for the variables specified in section 5.4. A sensitivity analysis that considers alternative assumptions about data missing not at random (MNAR) will be conducted. No missing data is anticipated for covariates included in the primary endpoint adjusted analysis, as these data were required for enrolment and randomization.

5.7 MULTIPLE TESTING

The sample size for this study was carefully selected to ensure an adequate number of participants for evaluating the antiretroviral activity of BIC/FTC/TAF. As such, no formal adjustments will be made to control the Type I error associated with planned secondary analyses. P-values from tests on endpoints unrelated to the antiretroviral activity of BIC/FTC/TAF may be provided for supportive purposes only. All statistical tests, apart from

the primary endpoint, will be two-sided unless otherwise specified. The significance level for each hypothesis and analysis will be set at $\alpha = 0.05$, unless stated otherwise.

6 SUMMARY OF STUDY DATA

The study data will be presented in the final report using tables and figures. Summary tables will be organized by data type and population (ITT/mITT and, if applicable, AT). Each table will have a title, footnote, and reference number. Continuous data will be summarized using the number of non-missing participants (n), mean, standard deviation, median, interquartile range (minimum and maximum), while categorical data will be summarized using the number of non-missing participants (n), frequency, and percentage values. The number of missing values for each variable will also be reported. Summary statistics will be stratified by treatment group. Continuous data will be analysed using either parametric or non-parametric methods, depending on the data distribution. Categorical data will be compared between groups using either chi-square or Fisher's exact tests.

6.1 PARTICIPANT DISPOSITION

6.1.1 Screening and allocation

A patient is considered a study participant once they screened and have meet the study eligibility criteria as well as having signed the Informed Consent; otherwise, they are excluded from the study for reason/s listed the exclusion criteria in section 4.2 of INSIGHT study protocol. As patient is randomized to a group (BIC or DTG), he/she is assigned a participant number and therefore considered enrolled (see Figure 1). We will present an overview of the time-dependent recruitment rates and ratios as a graph with y axis being the enrolment ratio or rate and the x-axis is year-month; a mock graphical presentation is shown in Figure 2. The enrolment ratio is calculated as cumulated screenings divided by enrolments while the enrolment rate is calculated as randomized patients divided by the number of months of in recruitment time.

6.1.2 Follow-up

A study participant may be considered a completer for the following reasons specified in the Termination CRF as end of study and early study closure; otherwise, the participant is discontinued; listed as Lost-To-Follow-Up (may arise from relocating), withdrew consent (refuse further participation), death, investigator decision and other. Where required, further explanation will be provided for discontinued participants.

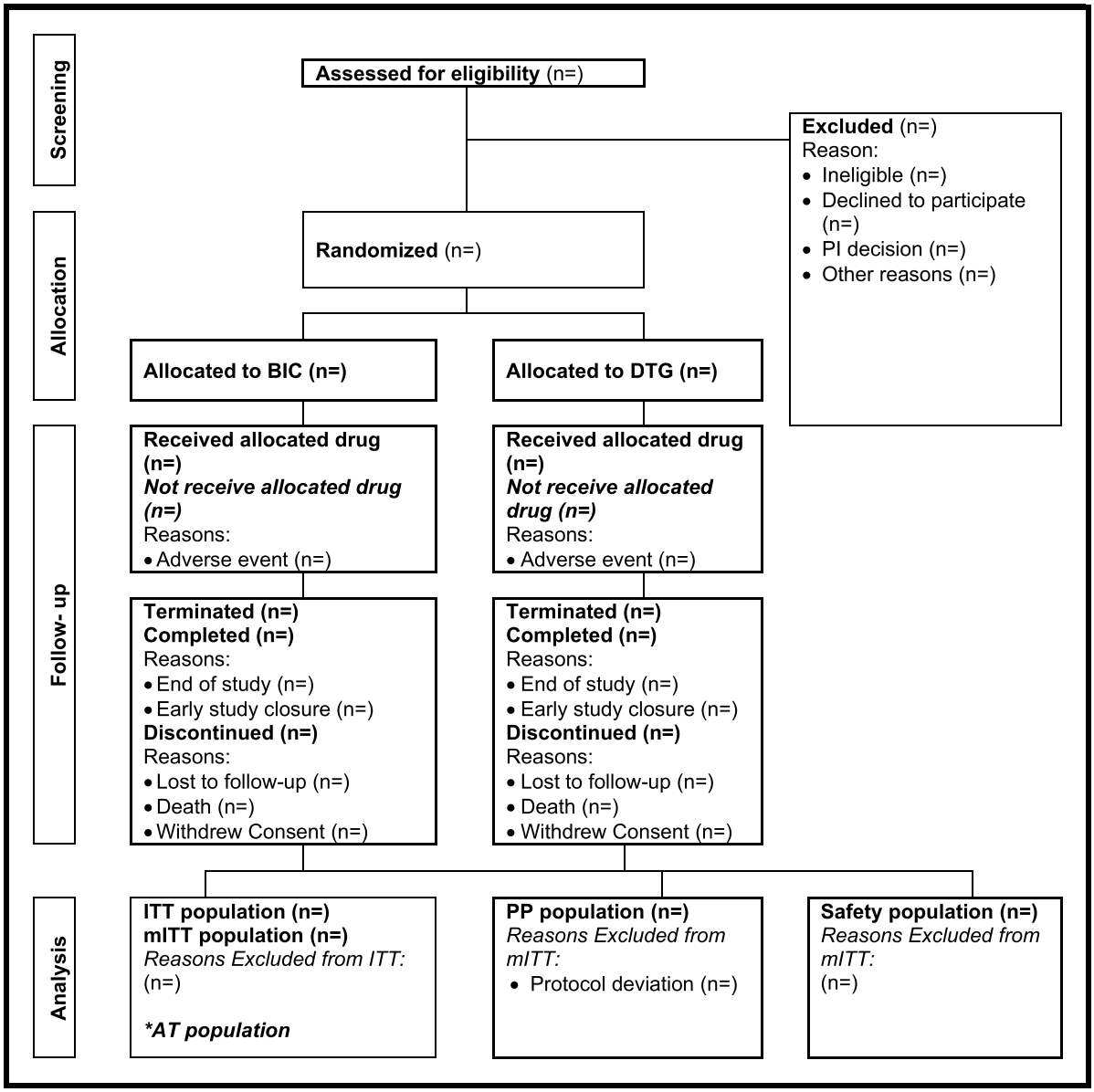

Figure 1: INSIGHT study skeleton CONSORT diagram

6.2 DEMOGRAPHIC AND BASELINE VARIABLES

Demographic and baseline characteristics will be summarized descriptively as indicated in section 6 of this SAP. Table 4 is a mock presentation of the statistics and it list all the demographic and baseline characteristics.

6.3 CONCURRENT ILLNESSES AND MEDICAL CONDITIONS

The number and percentage of participants having the medical histories or condition such as:

- Diabetes Mellitus
- Hypertension
- Coronary Artery Disease,
- Cerebrovascular accident
- Malignancy
- Epilepsy
- Asthma
- Peripheral Neuropathy
- Psychiatric condition
- Others*

**Other specified medical conditions will be standardized*

6.4 TREATMENT COMPLIANCE

Assessment of TB and ART compliance will be reporting adherence percentage as reported in the database. This percentage will be reported from enrolment to end of study.

7 STATISTICAL ANALYSES

The analysis of all clinical endpoints will be performed using the mITT and PP populations. The PP (and, if applicable, AT) population will be used for sensitivity analyses, unless otherwise specified. Analyses using the ITT population will also be performed. Safety population will be used for analyses of all safety outcomes while the PK population will be used for PK outcomes. A post-hoc sensitivity analysis using multiple imputations may also be conducted if deemed necessary. Further exploratory analysis which may be deemed appropriate to further characterize the endpoints by covariates and/or subgroups will be performed.

7.1 PRIMARY EFFICACY ANALYSIS

7.1.1 Unadjusted Analysis

The primary analysis to test this hypothesis will be conducted using a one-sample binomial exact test (normal approximation may also be used) to assess whether the proportion of participants with HIV-1 RNA levels <50 copies/mL at Week 24 is statistically significantly different from the prespecified response rate of 70%. The null and alternative hypotheses are stated as

H_0: $\pi \leq 0.70$ the true proportion of participants achieving viral suppression at week 24 is less than or equal to 70%)

H_A: $\pi > 0.70$ (the true proportion of participants achieving viral suppression at week 24 is greater than 70%).

The resulting analysis results will report for each analysis population used the number and percentage of participants with suppressed virologic response, the estimated standard error, upper 95% confidence interval and the one-sided p-value.

7.1.2 Exploratory subgroup analyses

Exploratory subgroup analyses will be conducted in a post-hoc manner to investigate whether any demographic or clinical characteristic variables may modify the effect of the viral suppression at week 24 and 48. The study population will be divided into subgroups categorical covariates based on age, sex, baseline HIV viral load, baseline CD4 cell count, adherence to ART and TB treatment, prior ART and TB treatment, co-morbidities, HIV and TB drug resistance, body mass index (BMI), duration of TB treatment, etc. The analysis will be done using logistic regression models or other appropriate statistical methods for binary endpoint. The results of the exploratory subgroup analyses will be interpreted with caution, as they may be subject to confounding, interaction, or heterogeneity of treatment effects.

7.1.3 Adjusted analysis

The primary endpoint will further be assessed using a logistic regression model that adjust for gender, age, baseline HIV viral load and baseline CD4 cell count.

7.2 ANALYSES OF SECONDARY ENDPOINTS

a. Viral suppression rates (HIV-1 RNA <50 copies/mL) at weeks 12, 24 and 48 in the DTG arm and at 12 and 48 weeks in the BIC arm.

The proportion of patients with viral suppression (HIV-1 RNA <50 copies/mL) at each time point will be calculated for each treatment arm by dividing the number of patients with HIV-1 RNA <50 copies/mL by the total number of patients in the DTG and BIC arms, respectively. The results will report the proportion along with its 95% two-sided confidence interval. Further assessment of viral suppression rates over time using a longitudinal generalised linear model with a logit link. The parameters of this model will be estimated using generalized estimating equation that accounts for within-patient correlation.

b. PK of BIC when given twice daily and co-administered with Rifampicin during TB treatment vs when given alone after TB treatment completion.

The Pharmacokinetic Analysis Plan as in the INSIGHT protocol (Version 3.0) will be followed. The parameters and analysis approach are also summarised in Table 3.

c. Incidence of TB associated IRIS through week 24, by Arm

The analysis for the incidence of TB-associated IRIS will use descriptive statistics to summarize the incidence of TB-associated IRIS through week 24, separately for each arm (DTG and BIC). For each TB-associated IRIS, binary variable as recorded in the study IRIS dataset, the number, and percentages (95% CI) of patients who have IRIS will be presented as well as listing the number of IRIS episodes. In a case where some participants have multiple occurrences of the same TB-associated IRIS, appropriate methods that account for within participant dependency will be used.

d. Grade 3 or higher AEs, SAEs; clinician-initiated treatment interruptions or switches through week 48.

The analysis for these binary outcomes of adverse events that are categorised as 1) grade 3 or higher, and 2) SAE as well as 3) treatment interruptions or switches through week 48 will use descriptive statistics to summarize the incidence separately for each arm. For each of these outcomes, the proportion and their 95% CI will be presented. The analysis will use methods that account for within participant dependency given that it is highly likely to realise more than occurrence of each outcome for a single participant.

e. Frequency of ART drug resistance mutations in participants with detectable viral load at weeks 24 and 48.

This is a descriptive analysis and will calculate the frequency of participants with ART drug resistance mutations at weeks 24 and 48. The report will describe each specific mutation (to NRTI, NNRTI, or INSTI) and its frequency.

7.3 Analyses Exploratory Endpoints

Exploratory analyses are hypothesis-generating rather than hypothesis-confirming, and any significant findings should be confirmed in future studies. The results will be presented using a descriptive summary table.

a. PK of FTC, TAF, and intracellular TFV-DP when given twice daily and co-administered with Rifampicin during TB treatment vs when given alone after TB treatment completion.
b. PK of TB drugs
c. Effects of pharmacogenetics of drug metabolising enzymes or drug transporters (e.g., UGT1A1, CYP3A, p-gp) on BIC/FTC/TAF/DTG PK
d. Association between hair PK and virologic suppression

Descriptive statistics to summarize the data for these endpoints as described in section 6 of this SAP, such as mean, median, standard deviation, and range. Endpoints a) and b) will

follow Pharmacokinetic Analysis Plan as indicated in the INSIGHT study protocol. Endpoint c) will make use of either analysis of variance (ANOVA) or analysis of covariance (ANCOVA) to compare the PK parameters between different treatment groups while endpoint d) uses model-based approach to analyze the association between hair PK and virologic suppression.

8 SAFETY ANALYSES

This analysis will report the adverse events attributes as per study progress, data, and safety monitoring plan. Summaries and listings reporting the number of events and number of participants in each arm will be presented for

- adverse events severity
- serious adverse event (defined by ICH)
- adverse events system organ class and preferred term – MEDRA coding
- serious adverse events system organ class and preferred term – MEDRA coding
- relationship of adverse events system organ class and preferred term and TB Drug
- relationship of adverse events system organ class and preferred term and ART Drug

9 PHARMACOKINETICS

The pharmacokinetic (PK) parameters to be analyzed, as well as the approach to data summaries and analyses, are described in the table below. The PK analysis plan provides detailed information regarding the analysis plans for PK and PD objectives.

Table 3: Pharmacokinetic parameters and their description

PARAMETER	DESCRIPTION
PK ASSESSMENTS	Performed in the BIC arm for participants who provided informed consent. PK samples in the control arm may be stored for later analysis.
PK PARAMETERS	Ct, Cmax, AUC will be computed for all subjects who undergo semi-intensive sampling.
ANALYTES	BIC, TAF, intracellular TFV-DP and DTG.
PK ESTIMATION	Nonlinear model using standard noncompartmental methods (WinNonlin® software).
DESCRIPTIVE STATISTICS	n, mean, SD, %CV, minimum, median, maximum, Q1, Q3, geometric mean, and its 95% CI will be calculated.
GEOMETRIC MEAN RATIOS	Generated for Ct, Cmax, AUC to compare these parameters during TB treatment vs. without concurrent TB treatment.

BLQ VALUES	The number of subjects with values of BLQ will be presented and treated as missing data.
POPULATION PK MODEL	Developed using data from both the semi-intensive PK sub-study and the sparse sampling in the overall study population to describe the PK in the larger population and assess determinants of variability in trough concentrations.

10 REPORTING CONVENTIONS

P-values greater than or equal to 0.001 will be reported to three decimal places, otherwise as <0.001. The mean, standard deviation, and other statistics, except for quantiles, will be reported to one more decimal place than the original data. Quantiles, such as the median, minimum, and maximum, will use the same number of decimal places as the original data. Estimated parameters that are not on the same scale as raw observations, such as regression coefficients, will be reported to three significant figures.

11 QUALITY ASSURANCE OF STATISTICAL PROGRAMMING

The quality of the statistical programming for INSIGHT study will be ensured by following the best practices and standards for coding, documentation, validation, and review which are documented in the Standard operating procedure for statistical analysis or output version 4. The main objectives of the quality assurance measures are to ensure that the code is clear, consistent, accurate, and reproducible.

The analysis code will be written in SAS and will follow the naming conventions, indentation rules, and commenting guidelines as specified in the statistical analysis or output SOP. The code will be organized into modular scripts that perform specific tasks, such as data manipulation, analysis, or reporting. The code will be stored in a version-controlled repository that tracks the changes and allows collaboration among the programmers.

The analysis code will be documented with sufficient comments and metadata to explain the purpose, inputs, outputs, assumptions, and logic of each script. The code will also include references to the relevant sections of the statistical analysis plan (SAP), the clinical study report (CSR), or other sources that define the analysis specifications. The code will also include error handling and logging mechanisms to capture any unexpected issues or warnings during execution.

The code will be validated by performing various checks and tests to ensure that the results are consistent with the SAP and CSR, and that there are no errors or discrepancies in the data or outputs. The validation process will include:

a) Checking the data quality and integrity by performing data cleaning, outlier detection, missing value imputation, and consistency checks.
b) Checking the analysis results by performing descriptive statistics, exploratory analysis, hypothesis testing, and sensitivity analysis.
c) Checking the output quality and format by performing output verification, formatting, labelling, and annotation.

The code will be reviewed by a second statistician within CAPRISA who will independently reproduce the primary analyses and summary statistics tables. The reviewing statistician will have an overview of the entire analyses and will explicitly check the code producing tables as well as any other pieces of code as desired. The review process will include:

a) Comparing the results from the original and reproduced analyses and resolving any discrepancies or issues.
b) Evaluating the code quality and readability by checking the adherence to the coding standards and documentation guidelines.
c) Providing feedback and suggestions for improvement or optimization of the code.

The code review will be documented with a summary report that describes the review process, findings, resolutions, and recommendations. The report will also include a sign-off from both the original and reviewing statisticians to confirm that the code meets the quality criteria and is ready for final submission.

12 REFERENCES

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13 TABLES AND FIGURES FOR PRIMARY ANALYSIS

SAS 9.4 software will be used to produce results for all the statistical analyses. R markdown and R software will be used to extract and report the resulting tables in the form of Tables, Listings, and Figure for inclusion in the main reports and/or manuscripts. Tables, listings, and figures presented in this SAP are using ITT/mITT analysis set, however, similar presentation will be followed for other analysis sets as guided by the SAP.

13.1 TABLES

13.1.1 Demographics and clinical characteristics

Table 4: Baseline characteristics of randomised participants

Variable - m	**BIC**	**DTG**	**All**
Primary Analysis Covariates			
Females, *n (%)*			
Age, *Median [IQR]*			
Age less than 50, *n (%)*			
HIV-1 RNA, *Median [IQR]*			
HIV-1 RNA copies/mL > 100 000, *n (%)*			
CD4 count, *Median [IQR]*			
CD4 count categories *n (%)*			
[At most 50]			
[Greater than 50 to 100]			
[Greater than 100 to 250]			
[Greater than 250]			
General Characteristics			
Black, n *(%)*			
Employed, n *(%)*			
Highest Education, *n (%)*			
[Primary]			
[Secondary]			
[Tertiary/college]			
Marital status, *n (%)*			
[Single]			
[In a relationship]			
[Living with stable partner]			
[Married]			
[Other]			

Contraception, *n (%)*			
[Injectable contraceptive]			
[Intrauterine device (IUC)]			
[Sterilisation]			
[Injectable contraceptive]			
[Not applicable]			
eGFR (mL/min), *Median [IQR]*			
Urea (mmol/L), *Median [IQR]*			
Creatinine (mu mol/L), *Median [IQR]*			
Amylase (IU/L), *Median [IQR]*			
ALT (IU/L), *Median [IQR]*			
AST (IU/L), *Median [IQR]*			
Bilirubin (IU/L), *Median [IQR]*			
Height (m), *Median [IQR]*			
Weight (kg), *Median [IQR]*			
BMI (kg/m^2), *Median [IQR]*			
Diastolic BP, *Median [IQR]*			
Systolic BP, *Median [IQR]*			
Respiratory rate, *Median [IQR]*			
Pulse, *Median [IQR]*			
Karnofsky score, *n (%)*			
[70 - Cares for self]			
[80 - Normal activity with effort]			
[90 - Carry on normal activity]			
[100 - Normal]			
TB Diagnosis			
Treatment duration prior to enrolment (days), Median [IQR]			
Pulmonary TB, *n (%)*			
Miliary TB, *n (%)*			
Extra-Pulmonary TB, *n (%)*			
GeneXpert, *n (%)*			
[Positive]			
[Negative]			
Sputum Smear, *n (%)*			
[Positive]			

[Negative]			
TB History			
Past TB History, *(%)*			
Site of TB *n (%)*			
[Site 1]			
[Site 2]			
[……]			
Diagnosis, *n (%)*			
[DSTB]			
[Pre-XDR]			
[XDR]			
[MDR]			
Treatment duration (weeks), Median [IQR]			

m – is the number of missing values of at least 1 participant and will be reported next to the variable name.
Sterilisation contraception – Tubal ligation, hysterectomy, laparoscopy, and other surgical procedure.

13.1.2 Primary outcome

Table 5: BIC ARM Viral suppression outcome at 24 weeks: results from unadjusted analysis

ITT/mITT (n=)	Rate (%)	Standard error	Upper 95% CI	One sided p-value
Viral Suppression				

CI - Confidence interval;

Table 6: BIC ARM Viral suppression outcome at 24 weeks: adjusted analysis

ITT/mITT (n=)	Rate (%)	Standard error	Upper 95% CI	One sided p-value
Viral Suppression				
Adjusted Covariates	**Odd ratio**	**Standard error**	**95% CI**	**Two sided p-value**
Gender				
Baseline Age				
Baseline viral load				
Baseline CD4 count				

CI - Confidence interval;

13.1.3 Secondary Analysis

A. Viral suppression rates (HIV-1 RNA <50 copies/mL) at weeks 12, 24 and 48 in the DTG arm and at 12 and 48 weeks in the BIC arm

Table 7: Viral suppression rates (HIV-1 RNA <50 copies/mL) at weeks 12, 24 and 48 in the DTG arm and at 12 and 48 weeks in the BIC arm.

ITT/mITT Viral suppression Time point Analysis (<50 copies/mL)	**DTG arm (n=)** n (%) (95% CI)	**BIC arm (n=)** n (%) (95% CI)
Week 12		
Week 24		
Week 48		

Table 8: Exploratory analysis of viral suppression rates over time using a longitudinal generalised linear model with a logit link.

	Hypothesis generating estimates and statistical significance	
Effects	**Estimate (95% CI)**	**Two sided p-value**
Intercept[1]		
Treatment		
Time[2]		
Treatment*Time[2]		
Other covariates		

[1]viral suppression rate; [2]categorical time in weeks

B. PK of BIC when given twice daily and co-administered with Rifampicin during TB treatment vs when given alone after TB treatment completion.

Table 9: PK parameters of BIC at steady state in the BIC + RIF and BIC alone groups

Parameter	**BIC + RIF (n=)**	**BIC alone (n=)**
C_{max} - ng/mL, Mean (SD)		
C_{min} - ng/mL, Mean (SD)		
AUC_{tau} - ng.h/mL, Mean (SD)		
Geometric mean ratio of C_{max} (95% CI)		
Geometric mean ratio of C_{min} (95% CI)		
Geometric mean ratio of AUC_{tau} (95% CI)		

Table 10: Descriptive statistics of BIC concentrations at different time points in the BIC + RIF and BIC alone groups

Time point	**BIC + RIF (n=)**	**BIC alone (n=)**
Pre-dose, n (%) BLQ		
Mean (SD) ng/mL		
%CV		
Min-Max ng/mL		
Q1-Q3 ng/mL		
Geometric mean (95% CI) ng/mL		
Post-dose, n (%) BLQ		
Mean (SD) ng/mL		
%CV		
Min-Max ng/mL		
Q1-Q3 ng/mL		
Geometric mean (95% CI) ng/mL		

C. Incidence of TB associated IRIS through week 24, by Arm.

Table 11: Incidence of TB associated IRIS through week 24, by Arm

TB-associated IRIS	DTG arm Estimate (95% CI)	BIC arm Estimate (95% CI)
Fever >38.5C for more than 5 days		
Chest X-Ray Findings: Worsening or new		
Intra-thoracic lymphadenopathy		
Pulmonary infiltrates		
Pleural effusions		
Worsening or new cervical lymphadenopathy		
Manifestations of other TB		
New onset seizure		
Worsening of respiratory symptoms		
New or worsening neurological symptoms		
New or worsening abdominal pain		
New onset ascites		
New onset hepatosplenomegaly		
Treatment necessary		
Steroids necessary		

D. Grade 3 or higher AEs, SAEs; clinician-initiated treatment interruptions or switches through week 48.

Table 12: Incidence of Grade 3 or higher AEs and SAEs, by Arm

Adverse Events	DTG arm Estimate (95% CI)	BIC arm Estimate (95% CI)
Grade 3 or higher AEs		
Serious AEs		

Table 13: Treatment interruption for ART per arm.

Treatment interruptions	DTG arm n (N)	BIC arm n (N)
Changes		
Temporarily withheld		
Permanently discontinued		

Measurements presented as n (N): n - is the number of events.; N - is the number of patients.

13.1.4 Other Tables

Table 14: Adherence for ART and TB (based on pill-count) per arm.

Medication	Adherence Attributes	DTG arm Estimate (95% CI)	BIC arm Estimate (95% CI)
TB	*Overall*		
	Above 95%		
	Below 95%		
ART	*Overall*		
	Above 95%		
	Below 95%		

Table 15: Neuropsychiatric assessment per arm

Neuropsychiatric assessment	BIC	DTG	All
***Anxiety score**, median (IQR)*			
***Depression score**, median (IQR)*			
***Sleep score**, median (IQR)*			

Table 16: Change in weight, BMI, Glucose, Cholesterol, and triglycerides

Week	Weight (kg)	BMI (kg/m²)	Glucose (mg/dL)	Cholesterol (mg/dL)	Triglycerides (mg/dL)
BIC, mean (Standard Error)					
4					
8					
12					
24					
32					
40					
48					
DTG, mean (Standard Error)					
4					
8					
12					
24					
32					
40					
48					

Table 17: TB outcome per arm

TB outcomes	BIC N (%)	DTG N (%)	ALL N (%)
Cure			
Treatment completion			
Death			
Treatment Failure			
Rif Resistance case			
Transferred Out			
Lost to follow-up			
MDR Case			
NT/Non -DS-TB			

Table 18: Adverse Event severity per arm

Severity	BIC n (N)	DTG n (N)	All n (N)
Grade 1			
Grade 2			
Grade 3			
Grade 4			
Grade 5			

n - is the number of events.; N - is the number of patients.

Table 19: Serious Adverse Event defined by ICH per arm.

ICH Definition	BIC n (N)	DTG n (N)	All n (N)
Results in death			
Persistent or significant disability or Incapacity			
In-patient hospitalization or prolongs hospitalization			
Life threatening at the time of occurrence			
Congenital anomaly or birth defect			
Important medical event or intervention therapy required			

n - is the number of events.; N - is the number of patients.

Table 20: Adverse events summary per arm

System Organ Class	Preferred Term (MEDRA Coding)	BIC n (N)	DTG n (N)	All n (N)
….				

n - is the number of events.; N - is the number of patients.

Table 21: Serious adverse events summary per arm

System Organ Class	Preferred Term (MEDRA Coding)	BIC n (N)	DTG n (N)	All n (N)
….				

n - is the number of events.; N - is the number of patients.

13.2 FIGURES

13.2.1 Recruitment rates graph

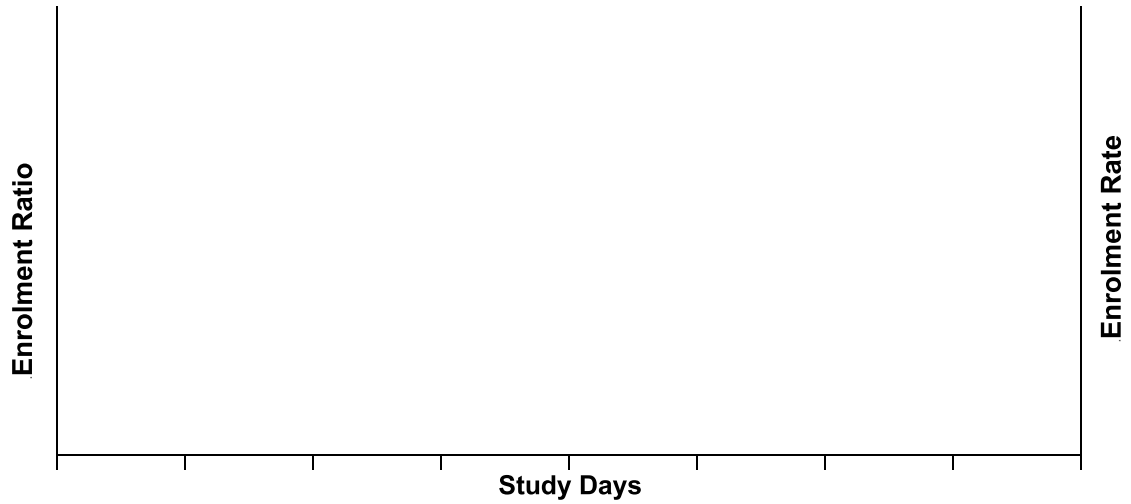

Figure 2: Enrolment ratio and rate graph